

**NARROWBAND UVB VERSUS NARROWBAND P-UVB IN
CASES OF CHRONIC PLAQUE TYPE PSORIASIS
– A MATCHED PAIR STUDY.**

**DISSERTATION SUBMITTED IN FULFILLMENT OF THE
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GUIDE

DR.C.R.SRINIVAS, MD

**DEPARTMENT OF DERMATOLOGY, VENEREOLOGY & LEPROSY
PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH
THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY
CHENNAI, TAMILNADU**

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DECLARATION

I hereby declare that this dissertation entitled **Narrowband UVB versus Narrowband P-UVB in cases of Chronic plaque type Psoriasis – A matched pair study** was prepared by me under the direct guidance and supervision of Professor Dr.C.R.Srinivas MD, PSG Institute of Medical Science & Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr. MGR Medical University in fulfillment of the University regulations for the award of MD degree in Dermatology, Venereology & Leprosy. This dissertation has not been submitted for the award of any other Degree or Diploma.

KARTHIKA NATARAJAN

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INTRODUCTION

Psoriasis is a chronic inflammatory skin condition of unknown aetiology which affects approximately 1-3% of the world's population^[1]. Clinically psoriasis manifests as erythematous plaques covered with silvery scales. It is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration consisting mostly of T lymphocytes and various endothelial vascular changes in the dermis such as angiogenesis, dilation and high endothelial venule formation. ^[2]Both genetic and environmental factors contribute to aetiology. Psoriasis is usually a life long disease with varying periods of remissions and exacerbations. The therapeutic options are wide ranging from topical to systemic agents and phototherapy. The goals of therapy should be to gain initial and rapid control of the disease process, achieve a longer duration of remission, provide a better quality of life by reducing the severity and minimizing the side effects.

Phototherapy is the use of non- ionising radiation as a treatment modality. In the past three decades , phototherapy has greatly influenced treatment concepts in dermatology. Photochemotherapy (PUVA) consists of absorption of non-ionizing radiation by an exogenous molecule. This substance is usually psoralen that is derived from the plant source *ammi majus*, *psoralea corylofolia*.

UV radiation has been used in the management of skin diseases such as psoriasis and atopic dermatitis. The prototypic skin disease showing a favourable response to UVB phototherapy is psoriasis. UVB Phototherapy are now believed to act by immunomodulatory effects on human skin and suppression of accelerated DNA synthesis in psoriatic epidermal cells and this is important for UV phototherapy. Narrow-band UVB(NbUVB; 311-313nm) has proved as effective as PUVA with minimal long term side effects such as carcinogenicity.

Since photochemotherapy entails the use of psoralen. It is associated with more side effects and cannot be administered to children. However, Narrow – band UVB is effective without the use of psoralen and so is gradually replacing photochemotherapy. There are certain cases which do not respond adequately to both PUVA and NbUVB. This study is undertaken to determine whether addition of psoralen makes Nb UVB more effective than NbUVB without psoralen.

Aims and Objectives

To compare Narrowband UVB and Narrowband P-UVB in treatment of Chronic plaque type Psoriasis.

REVIEW OF LITERATURE

PSORIASIS

History

Psoriasis is one of the longest known illnesses of humans . Although the name psoriasis was not introduced for many years the actual condition of psoriasis was first talked of by the Greek physician ,Hippocrates who lived between 460 and 377 BC.Some scholars believe psoriasis to have been included among the skin conditions called tzaraat in the bible.The biblical term ‘lepra’ was applied to various cutaneous disorders including psoriasis, vitiligo, eczema, boils and alopecia areata.^[3]

The Roman sage Aureliues Cornelius Celsus is credited with the first clinical description of psoriasis.^[4]Galen was the first to use the term Psoriasis and Robert Willain in 1808 (1757-1812) recognized psoriasis as an independent disease.^[5]. Robert Willain identified two categories. Leprosa Graecorum was the term he used to describe the condition when the skin had scales.Psora Leprosa described the condition when it became eruptive.In 1841 Ferdinand Von Hebra, a Viennese Dermatologist definitely distinguished the clinical features of psoriasis from that of leprosy.

Epidemiological aspects:

Estimates of the occurrence of psoriasis in different parts of the world vary from

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0.1 to 3% ^[6,7]. Psoriasis can present at any age and can appear just after birth or in old age ^[8]. There is a bimodal age of onset, the first peak at 15 – 20 years of age and a second one at 55 – 60 years. A North Indian study found that the mean age of onset was higher for males than females (37 vs 29 years) ^[9]. Possession of certain HLA antigens, particularly HLA-Cw6, is associated with an earlier age of onset and a positive family history.

A high familial occurrence of psoriasis (7% - 36%) suggests that genetic factors play a role in its etiology ^[8,10-13]. Psoriasis occurs with almost equal frequency in males and females^[8]

Aetiopathogenesis :

Hypothesis of psoriasis pathogenesis have changed over the decades but its etiology still not known. ^[14]. With the availability of monoclonal antibodies the pattern of inflammatory infiltrate in the psoriatic lesion was characterized and evidence accumulated to suggest that psoriasis is a T cell mediated autoimmune chronic inflammatory disease.

1. Presence of clonal population of T cells in the dermis (CD4 T cells) and epidermis (CD8 T Cells) which may precede epidermal hyperplasia.

2. Prompt response to therapeutic agents specifically targeting T lymphocytes
eg. Cyclosporine.

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3. Increased expression of some adhesion molecules that promote leukocyte adherence, such as ICAM-1 and E-Selectin.

Regenerate Keratinocyte Differentiation in Psoriasis:

The increased keratinocyte proliferation in psoriasis is believed to be due to an increase in the proliferating cell compartment in the basal and suprabasal layer (about 10% of basal keratinocytes are cycling in normal skin, while in lesional skin this is up to 100%) rather than due to shortened cell cycle time. The transit from a basal keratinocyte to a desquamated cell takes 4 – 6 weeks in normal skin, but in psoriasis this occurs in only a few days^[15]. The result of this incomplete differentiation / parakeratosis is that the stratum corneum barrier is not formed correctly in psoriasis plaques resulting in a defective barrier and the shedding of stratum corneum fragments in large sheets of scales / flakes ^[15]

Genetic Factors :

Patients with psoriasis have an increased frequency of HLA-B13, HLA – B17 and HLA-Bw16^[16-18]. One of the most susceptible factor is the presence of HLA-Cw0602 ^[19]. The best established locus is PSORS1, which has been

identified in all genetic studies and accounts for 35% - 50% of the genetic liability to psoriasis.

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Immunopathogenesis of Psoriasis:

Both innate and acquired immunity contribute in pathogenesis ^[20] Psoriasis is an immunologically mediated disease caused by activation of T lymphocytes that elaborate a Th1 type of immune response.

In normal skin, there are a few T cells in the dermis (but none in the epidermis), a few myeloid (CD11C+) dendritic cells (DCs) in the dermis and langerhans cells mainly and relatively uniformly in the epidermis ^[15]

In Psoriasis lesions, T cells and dendritic cells form dense dermal aggregates, the number of DCs equaling or exceeding that of T cells. CD4 T cells are predominantly present in the upper dermis, CD8 T cells in all layers of the epidermis and myeloid DCs in the dermis and lower layers of the epidermis, while langerhans cells migrate into the upper spinous layer and neutrophils accumulate in small aggregates in the stratum corneum ^[15] While these leukocytes can enter the skin by transmigration through vessels, the resident leukocytes could also expand to create the infiltrate ^[21]

Possible steps in the pathogenesis of Psoriasis

1. T cell activation by presentation of antigen by the antigen presenting cell in the lymph nodes.

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2. T cell binding to the endothelium in the vasculature with subsequent migration into the skin.
3. T cell reactivation by a second exposure to antigen which occurs in the dermis or epidermis.
4. Production of cytokines by various effector cells and development of psoriasis
5. Transition of the autoimmune process to the joints and development of arthritis.

To generate a cutaneous T-cell response, antigen presenting cells (Langerhans cells in the epidermis) take up and process autoantigens and migrate to the regional lymph nodes. There, they come in contact with naive T lymphocytes (CD45RA⁺). Within an immunologic synapse, molecular interactions result in T-cell activation [22]

According to the putative theory, antigen-presenting cells present processed antigen bound to major-histocompatibility – complex (MHC) molecules to the T-cell receptor (TCR). MHC Class II molecules present antigen to CD4 + T cells,

whereas MHC Class I molecules present antigen to CD8⁺ T cells. Additional signals are transmitted through interactions of co-stimulatory molecules with their ligands such as CD2 with CD58, CD28 with either CD80 or CD86, or both. In

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addition, adhesive interactions (eg by integrins and their immunoglobulin superfamily ligands) also stabilize the immunologic synapse and transmit additional signals. Following the activating signals, T cells differentiate into CD45 RO⁺ memory T cells and express skin-homing receptor cutaneous lymphocyte – associated antigen (CLA). Once activated, T cells (CD45RO⁺ and CLA⁺) reenter the circulation and preferentially extravasate at sites of cutaneous inflammation. In the skin, on encountering the respective antigen, T cells exert their effector functions, which include the secretion of pro-inflammatory cytokines. Psoriasis is characterized by a chronically persisting response in effector T cells.

Recently, it was estimated that the entire normal skin surface contains twice the number of T cells in the circulation ^[21,23] There was also TNF- α induced endogeneous activation of DCs and non-lesional resident T cells in psoriatic patients ^[24] These findings suggest that the apparently normal skin of psoriatic susceptible patients already contains a cellular microenvironment which becomes self – perpetuating once the disease process is initiated by bacterial antigens or superantigens ^[25]

An alternative theory is that the innate immune system initiates the psoriatic lesion, but in the process, neoantigens, become exposed. These antigens induce an adaptive immune response that maintains the psoriatic lesion^[26] Thus, both the

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innate and adaptive immune systems triggered by environmental stimuli and/or putative psoriatic antigens could act synergistically to induce psoriasis in a genetically predisposed individual.

Triggering and Modifying Factors :

1. **Local Factors** – Psoriatic lesions tend to develop at sites of injury to the skin. The koebner phenomenon refers to the induction of lesions by cutaneous trauma^[27]

2. **Seasonal Variations**

Most patients experience worsening of their skin lesions during winter ^[6,7]

3. **Pregnancy**

Psoriasis may remit during pregnancy. This is due to increased IL–10 levels in the circulation

4. **Emotional Stress**

60% of patients describe stress as being a key exacerbator or trigger of their disease .

5. Infections

Upper respiratory tract infections and tonsillitis especially when caused by

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streptococci may cause a flare-up of existing psoriasis or may precipitate an attack of acute guttate psoriasis ^[28-30]. An abnormal group A streptococcal and infection may play an important role in the exacerbation of psoriasis ^[31]

6. Drugs

Many drugs can precipitate or exacerbate psoriasis particularly beta – blockers, lithium, anti-malarials, imiquimod, interferons, Non-steroidal anti-inflammatory drugs and Angiotensin converting enzyme inhibitors^[32-43]

7. Sunlight, Alcohol and smoking are other factors associated with exacerbation of psoriasis.

Clinical Features:

The characteristic clinical presentation of chronic plaque type psoriasis is erythematous, well defined, scaly papules and plaques. It can also present as small papules (guttate psoriasis) pustules (pustular psoriasis) and generalized erythema and scaling (erythrodermic psoriasis).

The scales are abundant, dry and silvery white or micaceous. Whiteness is due to the presence of air trapped in between the layers of scales. When these scales are scraped off, the stratum mucosum is exposed and is seen as a moist red surface (membrane of bulkeley) through which dilated capillaries

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can be seen as red spots. On further scraping these capillaries at the tips of elongated papillae are torn leading to multiple bleeding points. This is a characteristic feature of Auspitz sign. Psoriasis can be clinically classified as follows

1. Chronic plaque psoriasis
2. Guttate psoriasis
3. Pustular psoriasis
4. Exfoliative psoriasis
5. Psoriasis unguis
6. Mucous membrane psoriasis
7. Arthropathic psoriasis
8. Regional variations in psoriasis – Scalp, face, eyes, body, flexures, scrotum, napkin area, palms and soles.

Chronic plaque psoriasis is the commonest type, seen in 90% of patients. The extensor surfaces particularly of elbows and knees, lumbosacral area and back are commonly involved.

Investigations :

The diagnosis of psoriasis can usually be made on clinical grounds and biopsy is occasionally required. The histopathological features are

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1. Parakeratosis
2. Presence of 'microabscesses of Munro' in the horny layer
3. Absence of a granular layer
4. Regular elongation of rete ridges, their lower portion is thickened showing a camel foot like shape.
5. Dilated and tortuous capillaries in the papillae with edema and perivascular mononuclear cell infiltration.
6. Thinning of suprapapillary parts of the stratum malphigii with occasional presence of spongiform pustules.

Treatment :

The nature of the disease and its chronicity with periods of remissions and exacerbations should be explained to the patient. The topical and systemic agents may give symptomatic relief and may prolong remission.

Topical treatment includes emollients, tar, corticosteroids, anthralin, keratolytics, calcipotriene and tazarotene. Systemic therapies for moderate to severe psoriasis includes methotrexate, acitretin, cyclosporine and biologic agents.

Topical therapy

Topical corticosteroids

Topical corticosteroids remain the most widely prescribed treatment for psoriasis worldwide. The more potent agents provide rapid efficacy, cosmetic acceptability, and versatility in use. A systematic review has shown that potent and very potent topical steroids are more efficacious for psoriasis than are agents that have mild and moderate potency. A major limitation in the assessment of topical steroids is the short duration of clinical trials, which makes issues such as tachyphylaxis (loss of efficacy with ongoing therapy)

difficult to appraise. Additionally, local effects such as skin atrophy, telangiectasia, striae distensae, and purpura, and systemic effects such as iatrogenic Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression, are seen with extensive treatment; subclinical cutaneous atrophy occurs in a substantial proportion of patients receiving these treatments for 4 weeks or longer. These side-effects are most likely with high potency corticosteroids; guidelines restrict the use of such agents to no more than twice a day for up to two consecutive weeks (50 g maximum per week) and discourage their use on the face or intertriginous areas. To minimise

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complications, various innovative regimens are used, such as use at weekends only, combination with non-steroidal agents, and transition to products of weaker potency when initial clinical response has been obtained.

Vitamin D derivatives

Since their introduction in the early 1990s, these agents have become first-line therapy for plaque psoriasis, either as monotherapy or in combination. Initial clinical responses with these preparations are inevitably slower than with higher potency corticosteroid agents, but their longer-term safety profile makes them valuable for maintenance therapy. Currently, three topical vitamin D

compounds are available: calcitriol (the active metabolite of vitamin D) and its synthetic analogues, tacalcitol and calcipotriol. These derivatives, available as creams, ointments, or solutions, are generally applied once or twice daily. A proposed benefit of tacalcitol over calcipotriol has been its once-daily dosage, although recent findings showed that once-daily dosing of calcipotriol cream might have similar efficacy to twice-daily application. Calcitriol might have better tolerability than calcipotriol in treatment of easily irritated areas such as the face, hairline, and flexural areas. The major theoretical benefit of calcipotriol is its limited effect on calcium homeostasis, although all three vitamin D³

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derivatives have been shown to be safe when used in their respective dosage regimens for periods of up to 1 year. Lesional or perilesional skin irritation with vitamin D analogues, manifesting as pruritus, burning, oedema, peeling, dryness, and erythema, is seen in up to 35% of patients and seems to be reduced with ongoing treatment. Although clinically relevant hypercalcaemia and parathyroid hormone suppression are rarely seen, some authors still recommend that calcium concentrations in serum should be monitored in patients with decreased renal function and impaired calcium metabolism.

An undoubted benefit of vitamin D analogues is their value in combination therapy, thus allowing for a reduction in the dose and duration of other antipsoriatic agents (acitretin, ciclosporin, broadband-UVB, narrowband-UVB, and photochemotherapy [psoralens and UVA; PUVA] and, hence, potential to improve the risk-benefit ratio for these treatments. Furthermore, several studies have proven marked benefits of using vitamin D analogues in combination with topical corticosteroids in various maintenance regimens. For example, maintenance with a vitamin D analogue was shown to be safe and effective after an initial period of a combination regimen of corticosteroid in the morning and a vitamin D analogue at night. Also, the addition of calcipotriol ointment on

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weekdays to a weekend pulse-therapy regimen of potent corticosteroids might increase the duration of remission.

Additionally, interest in the corticosteroid-sparing ability of vitamin D analogues has facilitated the development of a new single agent first-line topical therapy for plaque psoriasis. Large, well-controlled studies have established the superior efficacy of a once-daily combination ointment containing calcipotriol and betamethasone dipropionate over use of either agent alone. Side-effects of

corticosteroids and vitamin D analogues are minimised in clinical use for up to 1 year by use of this combination

Tazarotene

Tazarotene is the only topical retinoid (vitamin A derivative) available for the treatment of plaque psoriasis. Available in gel or cream formulations, applied once daily, usually at bedtime, it is only moderately effective as monotherapy, and therefore is predominantly used in combination. For instance, vitamin D analogues and moderate or potent topical corticosteroids all provide an additive effect, with reduced steroid atrophogenicity. In clinical practice, tazarotene seems to be less effective than calcipotriol, with a greater incidence of local

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irritation (personal observations).

Because of its teratogenic potential, tazarotene is not given during pregnancy, and in women of childbearing potential should be restricted to localised plaques only. Up to 20% of patients have local skin irritation, which can be minimised with use of cream formulation, low concentration, application on alternate days, short contact (30 min to 1 h), mild cleansers, and combination therapy with a mid-potency topical steroid in the morning.

Dithranol

Although a mainstay of the treatment of psoriasis for over 80 years, the use of dithranol (also known as anthralin) has fallen steadily with the advent of more cosmetically acceptable drugs. Recent investigative work has revealed that dithranol's mechanism of action is via a direct effect on mitochondria. As monotherapy, it has lower efficacy than either topical corticosteroids or vitamin D3 derivatives. However, when used with UVB phototherapy in the regimen proposed by Ingram, greater improvement is seen than with UVB alone. The addition of intermittent high potency topical corticosteroids minimises irritation⁴³ and enhances efficacy without shortening duration of remission. Furthermore, twice-daily calcipotriol added to short-contact 2% dithranol

ointment markedly augments the efficacy and tolerability of dithranol.

Because it causes substantial skin irritation and staining of skin, clothing, and furniture, dithranol is best used in hospital or in day treatment centres. Short contact applications of high-dose dithranol for up to 30-60 min a day has shown similar efficacy to longer applications and even twice-daily calcitriol ointment. Application of triethanolamine after removal of dithranol might reduce irritation

and staining of the skin. Newer formulations of dithranol might allow better tolerance.

Coal tar

Coal tar, a mixture of thousands of compounds, has been used in the treatment of psoriasis for more than a century. Available in ointments, shampoos, and solutions, crude coal tar is the most effective form available and, like dithranol, is commonly used in hospital or day-care settings. The combination of coal tar with UVB as described by Goeckerman has shown greater efficacy than UVB alone.. Skin irritation, folliculitis, odour, and staining of clothing limit coal tar's use as a routine outpatient treatment, in addition to its oncogenic potential.

Systemic treatments

Traditional systemic agents have been available for psoriasis since methotrexate was first approved by the US Food and Drug Administration in 1971 and remain the mainstay of treatment for patients with moderate to severe disease and those unresponsive to topical agents or phototherapy. Additionally, patients may be suited to systemic treatment if they have physical restrictions (eg, hand or foot psoriasis, associated psoriatic arthritis) or significant quality of life issues. All patients should receive a full physical examination; depending on the choice of agent, issues such as HIV status, presence of hepatitis, and previous

systemic cancers should be considered before initiating therapy .Biological therapies now provide new options for patients who previously were intolerant of or unresponsive to traditional systemic agents.

Methotrexate

Methotrexate, as a folic acid antagonist, interferes with purine synthesis and thus inhibits DNA synthesis and cell replication; it also has specific T-cell suppressive activities. Despite the advent of new therapies, methotrexate continues to play a central role as an affordable, gold standard treatment for

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recalcitrant psoriasis and psoriatic arthritis.

Despite its widespread use, only recently has the efficacy of methotrexate in treating moderate-to-severe psoriasis been established in head-to-head trials against ciclosporin. Methotrexate is usually prescribed orally in a once-weekly single-dose or three-divided-dose schedule over 24 h, after a 2.5-5 mg test dose, in doses ranging from 7.5 mg to 22.5 mg per week, pending clinical response. Oral folic acid 1.5 mg daily is added to prevent stomatitis and macrocytic anaemia and to decrease gastrointestinal symptoms, such as nausea, vomiting, and anorexia; however, it may reduce the efficacy of methotrexate. When

stability or adequate clearance is achieved, the lowest effective dose of methotrexate should be sought by tapering the dose slowly by about 2.5 mg per month.

Methotrexate has the potential for severe side-effects, necessitating careful selection and monitoring of patients. Firstly, because of its teratogenicity, methotrexate is absolutely contraindicated during pregnancy, and pregnancy should be avoided for at least 3 months after discontinuing treatment. Men whose partners are considering conception should also avoid methotrexate for this period of time. Bone marrow suppression is the most common cause of

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death attributable to this treatment; hence, appropriate screening every 1-3 months is essential. A rare complication of methotrexate therapy, pulmonary fibrosis, seems to be less common in psoriasis than in rheumatoid arthritis. By contrast, with long-term use, methotrexate seems more likely to cause liver fibrosis and cirrhosis (damage not reliably detected with liver enzymes or imaging) in patients with psoriasis than in those with rheumatoid arthritis. Current guidelines recommend a liver biopsy after a cumulative methotrexate dose of 1-5 g and then after every subsequent 1-5

Methotrexate can also be used as combination therapy with ciclosporin, as described for rheumatoid arthritis, with little apparent increase in side-effects; this combination seems particularly prevalent in patients with concomitant psoriatic arthritis. The effectiveness of methotrexate in combination with tumour necrosis factor α (TNF α) blocking agents, as used in rheumatoid arthritis and psoriatic arthritis, has yet to be validated in psoriasis.

Retinoids

Oral retinoids (vitamin A derivatives) have been used in the treatment of psoriasis for the past two decades. These synthetic hormones bind to nuclear

retinoid receptors, thereby altering gene transcription and returning keratinocyte proliferation and differentiation to normal. The original third generation retinoid used for psoriasis, etretinate, was superseded by its natural metabolite, acitretin, which was shown to have similar efficacy with a better pharmacokinetic profile. As a monotherapy, treatment is normally started with a dose of 10-25 mg acitretin, with dose adjustments dependent on response and side-effects.

Systemic retinoids are especially effective in the treatment of erythrodermic and pustular variants of psoriasis. Since they are not immunosuppressive, retinoids might have a role in the treatment of psoriasis in children, patients with HIV infection, and those that are prone to cancer. Retinoids are considered excellent for use in combination with other treatments and when used with UVB or PUVA, their dose and the number of phototherapy treatments can be reduced, with the added benefit of a potential reduction in skin carcinogenesis. Furthermore, systemic retinoids can also be combined or used sequentially with most other systemic and biological agents.

Systemic retinoids should be considered with extreme caution in women of childbearing potential because of teratogenicity. Women taking acitretin should

avoid pregnancy during treatment with acitretin and for 2 years (3 years in the USA) afterwards. Alcohol re-esterifies acitretin to etretinate, a potent teratogen; therefore, women should be cautioned about alcohol consumption while on this treatment.

Systemic retinoid toxicity is similar to hypervitaminosis A; hence, mucocutaneous side-effects (eg, cheilitis, skin dryness, conjunctivitis, and hair loss) are common. Other side-effects include hyperlipidaemia (especially triglycerides), osteoporosis, ligamentous calcifications, and skeletal abnormalities, including diffuse idiopathic skeletal hyperostosis syndrome. Rare side-effects include retinoid hepatitis and pseudotumour cerebri.

Ciclosporin

Ciclosporin, as serendipitously discovered in 1979 during a study of its efficacy in arthritis, is a useful short-term treatment for moderate-to-severe psoriasis, but is less effective for active psoriatic arthritis. It is a macrocyclic immunosuppressant that binds immunophilin and inhibits the calcineurin phosphatase-initiated activation of T cells; it may also exert a direct effect on epidermal keratinocytes.

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Ciclosporin therapy is carefully tailored to the individual patient with severe inflammatory or recalcitrant psoriasis. The recommended initial dosage is 2.5 mg/kg per day, although very active disease can necessitate starting with higher doses; dose adjustments are then made every 2-4-weeks up to a maximum of 5 mg/kg per day. Ideally, therapy should be restricted to intermittent short courses

of 12 weeks duration. Ciclosporin is highly effective in inducing a rapid remission of psoriasis; longer-term treatment at doses of about 3 mg/kg per day effectively maintains remission.

Unlike methotrexate, ciclosporin is neither teratogenic nor myelosuppressive, but requires careful monitoring for nephrotoxicity and hypertension.. Additionally, an increased risk of non-melanoma skin cancer exists, especially in patients previously treated with PUVA. Ciclosporin may lead to treatable laboratory abnormalities (hyperlipidaemia, hypomagnesaemia, and hyperkalaemia), hypertrichosis, gum hyperplasia, and gastrointestinal and neurological disturbances. If concentrations of creatinine in serum increase above 30% from baseline, ciclosporin doses should be lowered accordingly. Early hypertension can be treated with a calcium channel blocker (which may prevent nephrotoxicity), a thiazide diuretic, or an angiotensin-converting

enzyme inhibitor.

Ciclosporin is commonly used in combination or in rotation with other treatments for psoriasis, including low-dose methotrexate or acitretin and other agents such as mycophenolate mofetil, fumarates, sulfasalazine, and biological agents.

Fumaric acid esters

Oral fumaric acid esters (fumarates) have been used to treat severe psoriasis in Europe for more than 40 years, especially in Germany, after initially being reported on in 1959 by a German chemist who hypothesised and then demonstrated the benefits of fumarate therapy on his own psoriasis. Fumarates are naturally occurring molecules that link the urea and citric acid cycles, with their benefit in psoriasis now considered to be consequent mainly due to NFκB inhibition and T-cell apoptosis.

A commercially available mixture of four fumaric acid esters has been shown in a systematic review to be a highly effective treatment for psoriasis, with PASI reductions approaching those reported for methotrexate and ciclosporin. Unfortunately, despite an absence of severe adverse events, the fumarates may

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cause markedly unpleasant gastrointestinal symptoms, including abdominal cramps, diarrhoea, and nausea, as well as flushing, fatigue, and pruritus; these effects are probably seen more with high doses.

Biological agents

An appreciation of the immune pathways critical to the pathogenesis of psoriasis has led to the development of new agents that target these specific steps. Biological agents are recombinant molecules that are designed on the basis of genetic sequences from various organisms and that are often similar or identical to proteins produced by human beings. They include fusion proteins, recombinant proteins (eg, cytokines, selective receptors), and monoclonal antibodies, and are common treatments for autoimmune diseases such as rheumatoid arthritis and Crohn's disease (table 3). Psoriasis, a more common systemic disease with similar quality-of-life issues, has finally joined the biological revolution.

T-cell agents

Alefacept

Alefacept¹¹² was the first biological agent specifically designed and approved

for the treatment of psoriasis (in 2003, in the USA). It is a human leucocyte function associated antigen-3/IgG1 fusion (recombinant) protein that binds to CD2 on memory effector T cells, selectively interfering with the function of antigen presenting cells and, hence, T-cell activation. An additional and

important mechanism of action is apoptosis of memory-effector CD45RO-positive T cells in the skin. 20% of patients achieve a 75% reduction in PASI (PASI 75) after a 12-week cycle of weekly intramuscular injections of alefacept. Furthermore, a small proportion of patients have maintained a lengthy clinical response after the cessation of treatment (median duration 241 days). Improvement in psoriasis seems to correlate with a reduction in the number of memory-effector CD45RO-positive T cells in peripheral blood. Subsets of CD4-positive and CDS-positive T cells in peripheral blood are monitored on a fortnightly basis during the 12-week treatment cycles. Toxic effects on organs such as those seen with methotrexate, ciclosporin, and retinoids, are virtually absent.

Efalizumab

Efalizumab is a humanised monoclonal antibody that binds to the α subunit (CD11a) of leucocyte function associated antigen-1, thereby inhibiting

activation of T cells and adhesion between T cells and endothelial cells, which prevents circulating T cells from entering the skin. It is administered as a weekly subcutaneous injection, at 0.7 mg/kg for the first dose and 1 mg/kg thereafter. The most frequent short-term adverse effect is a flu-like syndrome

occurring in the first 2 weeks of treatment. The only toxic effect on organs seems to be rare occurrences of thrombocytopenia and haemolytic anaemia, necessitating monitoring of platelet counts.

Up to 20% of patients may develop a transient papular flare of psoriasis on the trunk and body folds, which is easily managed with topical therapy. However, a more striking generalised inflammatory flare occurs in up to 5% of patients, particularly those who are not responsive to therapy at 6-10 weeks after starting. Such flares might necessitate active intervention with systemic therapies such as methotrexate or ciclosporin or discontinuation of efalizumab.

TNF α inhibitors

Etanercept

Etanercept, a human recombinant TNF receptor p75 protein that binds to TNF α and β , is self-administered subcutaneously at a dose of 25 mg twice weekly

Very importantly, etanercept also relieves fatigue and symptoms of depression in patients with moderate-to-severe psoriasis. Etanercept is highly effective in psoriatic arthritis, with a reduction in the signs and symptoms of joint disease in

73-87% of patients at 12 weeks of treatment, with a parallel inhibition of radiographic progression of disease.

Infliximab

Infliximab is a chimeric monoclonal antibody that binds to and neutralises the activity of TNF α . In psoriasis, infliximab is given as an intravenous infusion, optimally in a dose of 5 mg/kg over 2-3 h at weeks 0, 2, and 6, and at regular 8-week intervals thereafter.

Adalimumab

Adalimumab is a fully human, anti-TNF α monoclonal antibody, self-administered subcutaneously in a dose of 40 mg on alternate weeks. As with the other anti-TNF α agents, structural changes on radiographs in patients with joint disease were prevented and disability significantly reduced. Patients had substantial improvements in their quality of life.

Side-effects

Data from clinical and post-marketing studies on these agents are predominantly derived from non-psoriasis patients and may not be applicable to psoriasis and psoriatic arthritis due to different comorbidities in this patient population, as well as the fact that overwhelmingly psoriasis and psoriatic arthritis patients are treated with monotherapy. In a recent meta-analysis of nine clinical trials using infliximab and adalimumab for rheumatoid arthritis, the authors emphasised the need for vigilance with respect to cancer and serious infections. Traditionally, because of the role of TNF α in granuloma formation, infections such as tuberculosis, histoplasmosis, and coccidioidomycosis require careful monitoring, with appropriate tuberculosis screening indicated in all patients before treatment with TNF α antagonists.

Other important issues common to this class of agents are rare instances of demyelinating conditions, including optic neuritis; and the exacerbation of cardiac failure in patients with a history of moderate to severe cardiac failure. The incidence of infections is possibly slightly greater with the two antibodies, infliximab and adalimumab, than with the fusion protein etanercept. Liver

toxicity should also be considered; recently completed phase III studies with infliximab showed that about 5% of patients had substantial (fivefold) increases in hepatic enzymes.

Future treatments

Although biological treatments have been a great advance in the management of psoriasis, their exact place in the hierarchy of systemic therapies will not be known until controlled trials have compared them against each other and with traditional approaches.

Research over the next decade will reveal new, specifically targeted biological therapies for the management of inflammatory immune-mediated diseases, including psoriasis. Anti-interleukin 12/23 agents have shown great promise in phase II and III studies, with significant clinical improvement noted in psoriasis after a single subcutaneous injection. Other cytokines identified as key proinflammatory determinants of psoriasis will also be targeted with opportunity for regulatory cytokine approaches, such as introducing Th2 cytokines (including interleukin 4 and interleukin 10) to restore the Th1/Th2 balance in what is essentially a Th1 disease. Pan-selectin and T-cell-specific

targeting are other potential approaches to psoriasis management. Small molecule technology might facilitate the administration of oral as opposed to injectable agents targeting TNF α and T-cell activation and signalling pathways.

New generation systemic calcineurin inhibitors such as pimecrolimus seem to be effective with negligible side-effects, such as hypertension or nephrotoxicity, over the course of 12-week studies. However, concerns about a possible increased risk of lymphoproliferative disease have delayed the further development of oral pimecrolimus. Another oral calcineurin inhibitor, ISA247, was tested for 12 weeks in psoriasis, resulting in 67% of patients in the 1-5 mg/kg per day dose group achieving PASI 75. Serum creatinine increased in patients treated with ISA247 1.5 mg/kg/day but remained within the normal range.¹⁴¹ An enteric-coated formulation of a single active fumarate, dimethylfumarate, has been shown to be highly promising and less toxic than fumarates. Pharmacogenetics has shown that polymorphisms in thymidilate synthetase, a key enzyme in the methotrexate metabolic pathway, might predict response to and side-effects from methotrexate in psoriasis. Polymorphisms in the gene for vascular endothelial growth factor could predict patients' responses to systemic retinoid treatment. We predict that the research interest in

angiogenesis in psoriasis will lead to the selective targeting of angiogenic factors, such as vascular endothelial growth factor, as is already happening in oncology. In the midst of this innovation, it should be acknowledged that to enhance the efficacy and reduce the side-effects of traditional systemic treatments is of pharmacoeconomic interest.

Phototherapy and photo chemotherapy play a major role in chronic psoriasis. The mechanism of action of ultraviolet B (311 – 313 nm) seems to be depletion of T cells, particularly those in the epidermis by apoptosis and a shift from Th1 to Th2 immune response in lesions. UVB phototherapy can be combined with prior application of coal tar. Patients of stable psoriasis with more than 20% body surface area affection can be treated with Narrow-band UVB. PUVA in psoriasis acts by suppressing DNA synthesis and cellular proliferation and inducing apoptosis of cutaneous lymphocytes. The 308nm excimer laser emits a monochromatic and coherent beam in the UVB spectrum and delivers high fluencies selectively to a lesion while sparing the surrounding healthy skin. ^[44] Physical treatments, such as the excimer and pulsed dye lasers, might be useful treatment modalities for localised, recalcitrant plaques of psoriasis. The excimer laser delivers high-energy 308 nm monochromatic UVR and has advantages over conventional UVR sources in that surrounding (normal) skin is untreated.

Side-effects include substantial erythema and blistering at treatment sites and residual hyperpigmentation. Studies of pulsed dye lasers in psoriasis report between 57% and 82% response rates, and remission may extend to 15 months. Psoriasis is currently an incurable disease that affects individuals differently. Maintenance of long-term safe control with important quality-of-life issues is paramount. The use of new treatments-physical, biological, or pharmaceutical-should not be a substitute for a detailed evaluation and discussion with patients to ascertain their expectations. Indeed, the management of psoriasis is still very much a mix of art and science.

PHOTOTHERAPY

History

The first report of the use of ‘phototherapy’ in the treatment of skin disorders dates from 1400BC from India when patients with vitiligo were given certain plant extracts (whose active ingredients included psoralens) and then exposed to the sun.^[45] The real interest in the use of ultraviolet (UV) irradiation in the treatment of various skin diseases started in the 19th century when Niels Finsen received the Nobel Prize (1903) for his therapeutic results with UV irradiation in lupus vulgaris, the only dermatologist ever to be awarded one.^[46] This marked the start of modern phototherapy. It was used in thermal stations for the treatment of tuberculosis, in the treatment of leg ulcers in wartime, and various other skin diseases.^[47] It was a very long journey from the use of plant extracts and sun exposure to treat vitiligo to the use of oral psoralens and total body UVA-irradiation cabins (PUVA) to treat various skin diseases. In a landmark development, in 1974 Parrish et al reported the useful role of high intensity UVA tubes in combination with oral psoralens in the treatment of psoriasis leading to what is now known as PUVA therapy.^[48] The history of UVB phototherapy is not as old as the history of photochemotherapy. Wiskemann introduced irradiation cabin with broad band UVB tubes in 1978 for the

treatment of psoriasis and uremic pruritus.^[49] However, broad band UVB phototherapy was less efficient for treating psoriasis than PUVA and so never achieved popularity. The breakthrough came after 1988 when narrow-band UVB (NB-UVB) phototherapy was introduced for the treatment of psoriasis by van Weelden et al and Green et al.^[50,51]

Phototherapy refers to the use of ultraviolet light for the treatment of various skin disorders. The ultraviolet light refers to the electromagnetic spectrum between 200nm to 400nm. The wavelength in the range of 200 to 290nm are referred to as UVC and this do not reach the earth's surface at sea level and the energy is absorbed by the ozone layer in the stratosphere. Moreover UVC region of spectrum is called Germicidal radiation which is lethal to the liable cells of the epidermis.

The next range between 290 to 320 nm is known as UVB and referred to as mid-UV or sunburn spectrum, wherein the most erythmogenic wavelengths of this spectrum reach the earth's surface . Most sunscreens work efficiently at minimizing the effects of this waveband. Infact, the sun protection factor (SPF) is actually based on testing against this waveband.

The long wave ultraviolet. A spectrum between 320- to 400 nm is referred to as black light because it is not visible to the human eye and causes certain

substances to emit visible fluorescence. UVA has been divided into UVA-I (340 to 400 nm) and UVA-II (320 to 340 nm) because the later band is more damaging to unsensitized skin than the longer wavelengths.

Response of skin to Ultraviolet radiation(UVR)

Skin is affected by UV and visible radiation that is absorbed by molecules in skin. In the first step, molecules in skin such as pyrimidine nucleotides, DNA (eg. Thymidine, cytosine) and urocanic acid absorb radiation. A light absorbing molecule is referred to as a chromophore. In some cases, the chromophore is an exogenous agent such as an ingested photosensitizing drug for example, tetra cycline or 8-methoxypsoralen. After absorbing the energy of the radiation, the chromophore is in an excited state. Although this highly energetic species exists for only a fraction of a second, a chemical change may occur during this time to transform the molecule into a photoproduct such as an oxidized membrane lipid ^[52,53] pyrimidine dimer ^[54] or psoralen-DNA adduct^[55]. The presence of photoproducts in cells provokes biochemical responses, beginning with signal transduction processes and further activate transcription factors such as AP-1 ^[56,57] and NF-KB^[58,59] and thereby initiate cellular synthesis of new proteins, for example, melanin^[60,61] cytokines^[62 - 64] and matrix metalloproteinase-1^[65,66] Other important processes such as repair of UV-

induced DNA damage also occur ^[67,68] These biochemical responses culminate in cellular effects such as proliferation, secretion of cytokines and apoptosis that are observed as acute skin responses.

The specific wavelengths of UV or visible radiation absorbed by these molecules are called absorption spectra. The wavelengths that have highest probability of absorption are called absorption maxima, λ_{max} and are used as identifying characteristics of a compound

(eg. DNA λ_{max} = 260 nm, Porphyrin λ_{max} = 400 to 420 nm)

UV Radiation Dosimetry

The basic unit of energy is the Joule (J)

Power is the rate of energy flow given in watts(W) or Joules per second ($W=J/s$)

The power delivered per unit area of surface is called Irradiance [$W/cm^2 = (J/s)$ per cm^2]

The total radiant energy delivered per unit area of skin surface is expressed as 'Exposure dose' or 'Fluence'. (Exposure dose = Irradiance x time = J/cm^2)

Acute effects of UVR

UVB causes considerable DNA damage in the basal layer, but UVA also

induce epidermal cyclobutane pyrimidine dimers with much higher doses. The tumor suppressor p53 protein is not detectable in normal human epidermis but is readily induced by a single exposure to UVR. This protein which acts as a transcription factor reduces cell cycle (G1) arrest to allow time for the repair of DNA photolesions thus minimizing the transfer of potentially carcinogenic mutations to daughter cells.

Erythema (Sun burn inflammation) is the most recognized acute cutaneous response to UVR and is associated with classical signs of inflammation namely, redness, warmth, pain and swelling. Erythema is UVR dose dependent, solar range UVB (300 nm and 313 nm) and UVA (365 nm) erythemas having similar slopes ,although the slopes for UVC (254 nm) and non solar UVB (280 nm) are much less steep ^[69]Erythema effectiveness declines rapidly with increasing wavelength, with for example 360 nm (UVA) radiation requiring 1280 times more energy than 300 nm (UVB) radiation to produce the same effect. Therefore, the relatively small UVB component & solar UVR accounts for the majority of its erythema effect. DNA is a major chromophore for erythema.

UVR exposure induces the synthesis and release of an extensive array of mediators including histamine, by-products of arachidonic metabolism, pro-

inflammatory and immuno-suppressive cytokines, chemokines, adhesion molecules, growth factors and neurotransmitters all of which profoundly influence the biological function of the skin.

UVR exposure suppresses cutaneous cell-mediated immunity in humans. The depletion of langerhans cells, the principle antigen-presenting cells in the epidermis, recruitment of macrophages into the dermis and epidermis and release of inflammatory mediators such as TNF - alpha, IL-10, TGF-beta, alpha-MSH and CGRP, are all important events in the initiation of immunosuppression. Susceptibility to UVR-induced immunosuppression appears to be skin-type dependant. Skin phototypes I/II are at greater risk of skin cancer and are also more readily immunosuppressed than patients of skin phototypes III/IV. DNA seems to be an important chromophore for UVR induced immunosuppression.

Tanning may be true melanogenesis known as delayed tanning or immediate pigment darkening. IPD is believed to result from photo-oxidation of existing melanins and redistribution of melanocytic melanosomes from a perinuclear position into the peripheral dendrites. Delayed tanning following UVR exposure is the result of increased epidermal melanin formation, the pigment becoming visible within days after UVB exposure. With exposure to longer

UVA wavelengths, tanning occurs earlier. UVB delayed tanning is associated with an increased in the activity of melanocytes while repeated doses are required to increase numbers.

The rate limiting enzyme in melanogenesis is tyrosinase and its activity correlates closely with the melanin content of cultured pigment cells and increases during tanning.

Chronic effects of UVR

A relationship between solar exposure and all types of skin cancer has been established and animal studies have shown that UV irradiation induces early epidermal apoptosis in the form of highly characteristic sunburn cells that are apparent within 30 min of exposure and maximal at 24 hours. DNA photodamage is the immediate acute effect that initiates a chain of molecular, mutational, cellular and immunologic events that lead to a skin tumor, especially non-melanoma skin cancer.

Photoaging as a result of UVR induced tissue degrading matrix metalloproteinases are well known and clinically characterized by dry deeply wrinkled, inelastic, leathery, telangiectatic skin and often with irregular pigmentation, freckling and lentigo formation (dermatohelosis)

PUVA Photochemotherapy

Psolaren plus UVA (PUVA) photochemotherapy is the photochemical interaction between psolaren and ultraviolet A.

Psolarens are naturally occurring compounds. Methoxsalen (8-methoxy psoralen) is obtained from the seeds of a plant *Ammi majus*. Psolarens intercalate between DNA base pairs without UV radiation ^[70 - 72]. Absorption of photons in the UVA range results in the formation of a 3,4 or 4,5 cyclobutane addition product with pyrimidine bases of native DNA. This intercalation of psoralens with epidermal DNA produces a suppression of both DNA synthesis and cell division which may be the possible therapeutic mechanism in psoriasis.

Oral psoralen is absorbed by the GI tract and increased photosensitivity is present one hour after the dose, reaches a peak at about 2 hours and disappears by eight hours^[73]. Psoralens are metabolized in the liver by hydroxylation and glucuronide formation and over 90% is excreted in the urine within 12 hours^[74]. Methoxsalen has a serum half-life of approximately one hour and is rapidly eliminated which prevents photosensitivity^[75].

PUVA causes photoconjugation of psoralens to DNA and subsequent suppression in mitosis, DNA synthesis, cell proliferation and immunological alterations. A decrease in the percentage of circulating T-lymphocytes

following PUVA treatment has been reported^[76]

Sources of UVA radiation

UVA sources commonly used for PUVA therapy are fluorescent lamps or high pressure metal halide lamps. The PUVA lamp has an emission peak at 352 nm and emits approximately 0.5% in the UVB range. UVA doses are given in J/Cm² and are measured with a photometer.

Narrow-Band UVB Phototherapy

A potential advance in UVB – based phototherapy has been the introduction of fluorescent bulbs (Philips model-TL-01) that deliver UVB in the range of 310 to 313 nm, with a peak at 312 nm.. It has a relatively narrow spectrum of emission which when compared with the older broad band UVB source has a reduction in erythemogenic wavelengths in the 290-305 nm range and 5-6 fold increased emission of the longer UVB wavelengths, thereby resulting in a higher phototherapy index for psoriasis.

Mechanism of action

In the skin , NB-UVB radiation is absorbed by DNA and urocanic acid and alters antigen presenting cell activity. NB-UVB is about 5-10 fold less potent than broad band UVB for erythema induction, hyperplasia, edema, sunburn cell formation and Langerhans cell depletion from the skin. It has a relatively more

suppressive effect than broad band UVB on systemic immune response as judged by natural killer cell activity, lymphoproliferation and cytokine responses. ^[77] The mechanism of action of NB-UVB phototherapy has not been completely understood. In psoriasis, lymphocyte proliferation and immune regulatory cytokine production is mediated by both Th1 (IL-2, IFN-g) and Th2 (IL-10) T-cell population ^[77,78]

Phototherapy Unit :

NB-UVB phototherapy cabins contain fluorescent TL-01 (100W) tubes as the source of irradiation. NB-UVB cabins available commercially either incorporate TL-01 alone or in combination with UVA tubes. Recently, shorter tubes of NB-UVB have also become available in small area treatment equipment (hand and foot unit, NB-UVB comb) for the therapy of localized body areas.

Dosing schedule

NB-UVB schedules can be tailored according to patient skin type and local experience. There are two regimens that are most commonly used, the first involves determination of the individual's minimum erythema dose (MED) by means of a separate bank of TL-01 tubes. Often 70% of the MED value is used for the first treatment; thereafter therapy is given three times or more in a week

with 40, 20 or 10% increments depending on local experience and skin type tolerance. Another approach, as commonly practiced in India, involves a standard dosing dose (280Mj), with stepwise increase (usually 20%) depending upon the patient's erythema response. In the photodermatoses, the approach is more cautious with only 10% incremental regimen in sunexposed sites^[78] In case of mild erythema, the irradiation dose is held constant for subsequent treatments or until resolution of symptoms. The goal of therapy is to achieve persistent asymptomatic erythema. In case of painful erythema with or without edema/ blistering, further treatment is withheld till the symptoms subside. After resolution of symptoms, the dose administered is 50% of the last dose and subsequent increments should be by 10%.

Narrow-band UVB in Psoriasis

The NB-UVB lamp was developed as a 'new' UVB phototherapy source with an emission spectrum within the therapeutic waveband for psoriasis phototherapy.

NB-UVB phototherapy has a higher ratio of therapeutic to erythemogenic activity, resulting in increased efficacy, reduced incidence of burning and longer remission. Results from two therapeutic action spectroscopy studies indicated that wavelengths of the range 295-320 nm are effective in clearing

psoriasis, whereas shorter wavelengths are more erythemogenic, and wavelengths longer than 320 are less therapeutic ^[79,80] Subsequent clinical studies have tended to report significantly greater improvement of psoriasis with NB-UVB including reduced incidence of burning episodes, increased efficacy and longer remission when compared with broad band sources^[81] When NB-UVB phototherapy and PUVA were compared, there was little overall difference in efficacy ^[82,83] Coven et al compared the therapeutic effectiveness of half-body exposures to NB-UVB or broad band UVB in moderate to severe psoriasis. ^[84] Clinical resolution was achieved in 86% of sites treated with NB-UVB vs. 73% treated with broad band UVB including faster clearing and more complete disease resolution. Although treatment with NB-UVB is reported to be highly effective in clearing psoriasis patients, whether this therapy represents a modest advance or a real breakthrough is not clear. If NB-UVB is to replace PUVA therapy in the treatment of more severe psoriasis, it must not only achieve a comparable clearance rate in psoriasis, but it must also maintain remission at a comparable frequency of treatment. At present, small studies do provide some hope in this respect.^[85]

The goal of phototherapy is complete clearance of all psoriatic lesions. Psoriasis, however, is a chronic disease and the remission induced by

UVB phototherapy is often transient. In a randomized, prospective, multicenter trial, post clearing phototherapy was found to significantly increase the disease free interval, indicating that patients may benefit from maintenance phototherapy(24). On the other hand, maintenance therapy results in a greater cumulative UVB dose, increasing the risk of skin cancer and photoaging. It is therefore preferable, if possible, to maintain remissions with other anti-psoriatic modalities. To minimize potential carcinogenic risks from chronic UVB phototherapy, a rotational therapeutic approach has been suggested.(25)

Oral psoralen with UVB for the treatment of psoriasis

Generally psoralen increases the sensitivity of skin to UVB and increases the minimal erythema dose [MED]. The light absorption spectrum for oral psoralen peaks at 325 nm^[86], but the absorption spectrum extends into the shorter wavelengths of ultraviolet light in the UVB range. PUVA treatment using 335-nm UVA is twice as effective as with 365-nm UVA with respect to both erythemogenicity and the cumulative dose required for clearing psoriasis; however, 335 nm and 365 nm are equally effective if delivered in equal erythema doses, suggesting that in human skin the antipsoriatic activity of 8-MOP parallels its erythemogenicity^[87]. The action spectrum for phototoxic

erythema after topical 8-MOP sensitization peaks around 330 nm ^[88].

Some, but not all, studies indicate that PUVB is more effective in treating psoriasis than UVB alone. In a study of 44 patients in which half are treated with PUVB and other half with PUVA, PUVB therapy is as effective as conventional PUVA in the treatment of stable, plaque-type psoriasis in patients with Fitzpatrick type-IV skin ^[89]. A significantly lower dose of UVB is required for clearance as compared with PUVA. In another study involving 100 patients, NbPUVB treatment of psoriasis is as effective as conventional PUVA ^[90]. A 1995 study found PUVB and UVB phototherapy equally efficacious in the treatment of psoriasis; however, those areas of the body treated with PUVA responded more rapidly and to a greater extent than areas exposed to UVB ^[91].

Oral psoralen works with NbUVB for the treatment of psoriasis

Some studies indicate that psoralen seems to work synergistically with 311-nm UVB (NbPUVB). The effect of psoralen in combination with nbPUVB has been studied in five subjects with normal skin and ten patients with psoriasis involving both forearms ^[92]. Treatment with oral 8-MOP augments the UVB erythema response at 6 hours after irradiation, but has no effect at 24-72 hours. In eight of the nine patients who complete the trial, lesions of psoriasis

on the arms treated with PUVB clear before lesions on the arms treated with UVB alone. This study has shown that psoralen in combination with UVB has an erythema effect on normal skin and a therapeutic effect in psoriasis that is greater than the response to UVB alone.

Materials and Methods

Seventeen patients of chronic plaque type psoriasis were enrolled in our study. A Baseline Total lesional severity scale (TLSS) to assess erythema, scaling and thickness were calculated and minimal erythema dose (MED) was determined for all the patients. MED was determined by standard method. A template with 10 apertures of $1\frac{1}{2} \times 1\frac{1}{2} \text{ cm}^2$ were made over the back of a cotton suit. Cotton flaps were made over the apertures enabling us to either shut or keep the apertures open by using Velcro. The source of Narrow-band UVB was the whole body phototherapy unit with 24 Philips TL -01 bulbs (V Care medical services Pvt Ltd). To determine MED a single panel in the whole body unit with 6 bulbs were used. All the apertures were kept opened and the back was irradiated with 250mj of Narrow-band-UVB. The first aperture was closed and the remaining apertures were then closed one after the other after delivering 50mj more than the previous aperture. The dosage schedule for Narrow-band-UVB were 250mj, 300mj, 350mj, 400mj, 450mj, 500mj, 550mj, 600mj, 650mj and 700mj. The readings were taken 24hrs after exposure. The dose at which the minimal perceptible erythema found was considered as MED.

For every patient, two clinically characteristic lesions for assessment were

selected on either side of the body. Narrow-bandUVB was given on right half of the body and the left half of the body was covered using a suite which covered one half of the body. Oral psoralen at a dose of 0.5mg/kg body weight was administered immediately to the patient and two hours later patients were exposed to narrowband UVB on the left half of the body while the right half was covered using the same suite. The initial dose of starting the treatment was taken as 70% of MED. The dose was gradually increased at the rate of 10% increment of the previous dose. The treatment was then given thrice weekly over a period of five weeks thereby completing a total of 15 sittings and the TLSS scoring was determined at the end of 5th, 10th, and 15th sittings respectively.

Inclusion criteria:

Chronic plaque type psoriasis, patients not on other modalities of treatment with minimum three weeks of wash off period and body involvement more than 20%.

Exclusion criteria:

Unstable psoriasis, erythrodermic psoriasis, pustular psoriasis, pregnancy, lactation, children under 12 years and body involvement <20% body surface

area.

Statistical analysis

For each patient an average score of erythema , scaling and thickness were calculated for NbUVB as well as NbPUVB at the end of 5,10 and 15 sessions.

These values were compared using ***WILCOXON TEST***. P value < 0.05 was considered as statistically significant

Results

A total of seventeen patients were studied. The age range of the patients were between 31 years to 70 years with the mean age of 49 years. Of the seventeen patients, 15 were men and 2 were women. The duration of psoriasis varied between 2 years to 28 years with mean duration of 15 years. All these patients belonged to skin type IV / V

The Minimal Erythema dose varied between 250mj to 950mj with mean of 457mj. (Table I)

Of the seventeen patients, thirteen completed the study ,one patient was lost for follow-up ,three patients [2 patients by the end of 4th treatment and 1 patient by the end of 8th treatment] could not continue due to aggravation of psoriasis. The score of the patients who aggravated are shown in Table III

The severity of the index lesion according to TLSS scoring before treatment and after five, ten and fifteen treatments were recorded as shown in table-I. The values when compared using Wilcoxon test (p value < 0.05) was considered as statistically significant. The statistical analysis is shown in Table II

The total TLSS score of fourteen completed patients at the end of five sittings is 132 (mean - 9.42) for NbUVB and 127(mean 9.07) for NbPUVB. The difference was not statistically significant. At the end of ten treatments the mean value was 5.76 for NbUVB and 4.92 for NbPUVB.

There was statistical significance at this point [p value = 0.006]. However by the end of our study, after fifteen treatments the mean value for NbUVB and Nb-PUVB were 3.0 and 2.76 respectively which were statistically not significant. Minimal side effects like erythema, pigmentation and pruritus were encountered during treatment as shown in Table IV

Table I

				TLS Scoring [Erythema (0-5) + Scaling (0-5) + Plaque elevation (0-5)]							
S.No	Age	Sex	MED	Baseline		After 5 Treatments		After 10 Treatments		After 15 Treatments	
				NbUVB	PNbUVB	NbUVB	PNbUVB	NbUVB	PNbUVB	NbUVB	PNbUVB
1	37	Male	750mj	13	13	9	9	5	5	2	3
2	62	Male	500mj	12	12	8	7	4	2	2	0
3	31	Male	500mj	15	15	12	11	7	5	3	3
4	70	Male	300mj	13	13	9	8	5	5	2	1
5	69	Male	950mj	14	14	11	8	9	7	7	7
6	57	Male	500mj	12	12	7	8	4	4	2	1
7	54	Male	250mj	15	15	13	11	8	7	5	6
8	34	Male	450mj	13	13	7	8	6	5	4	4
9	33	Male	300mj	13	13	8	8	5	5	4	2
10	59	Male	400mj	14	14	10	9	6	5	1	3
11	46	Male	500mj	13	13	10	9	6	5	1	3
12	51	Male	350mj	15	15	9	9	4	4	2	2
13	35	Female	300mj	14	14	8	10	7	7	3	2
14	48	Male	350mj	13	13	11	12	-	-	-	-
Mean	49.0 0		457.1 4	13.50	13.50	9.42	9.07	5.76	4.92	3.00	2.76

NbUVB : Narrow band ultra-violet B

NbPUVB : Psoralen + Narrow band ultra-violet B

Table II**Paired Samples Statistics**

		Mean	N	Standard Deviation	T Value	p Value
Pair 1 (Base line)	NbUVB	13.5000a	14	1.01905	-	-
	NbPUVB	13.5000a	14	1.01905		
Pair 2 (After 5 Sessions)	NbUVB	9.4286	14	1.82775	1.000	0.336
	NbPUVB	9.0714	14	1.43925		
Pair 3 (After 10 Sessions)	NbUVB	5.8462	13	1.57301	3.333	0.006
	NbPUVB	5.0769	13	1.38212		
Pair 4 (After 15 Sessions)	NbUVB	2.9231	13	1.70595	.210	0.837
	NbPUVB	2.8462	13	1.95133		

Table III**3 patients of aggravation**

S.NO	AGE	SEX	MED	Number of completed treatments	Base line		After four treatments		After eight treatments	
					Nb UVB	Nb PUVB	Nb UVB	Nb PUVB	Nb UVB	Nb PUVB
1	52	Male	300mj	4	12	12	13	14	-	-
2	25	Male	250mj	4	13	13	14	15	-	-
3	48	Male	350mj	8	13	13	11	12	15	15

Table IV**Side effects**

Adverse reactions	Number of patients
Generalized Pigmentation	9 / 13 (69.23 %)
Burning / Erythema	4 / 13 (30.77 %)
Pruritus	6 / 13 (46.15 %)
Lichenoid eruptions	1 / 13 (7.69 %)

MED DETERMINATION



READING AFTER 24 HOURS



BASE LINE – BEFORE TREATMENT

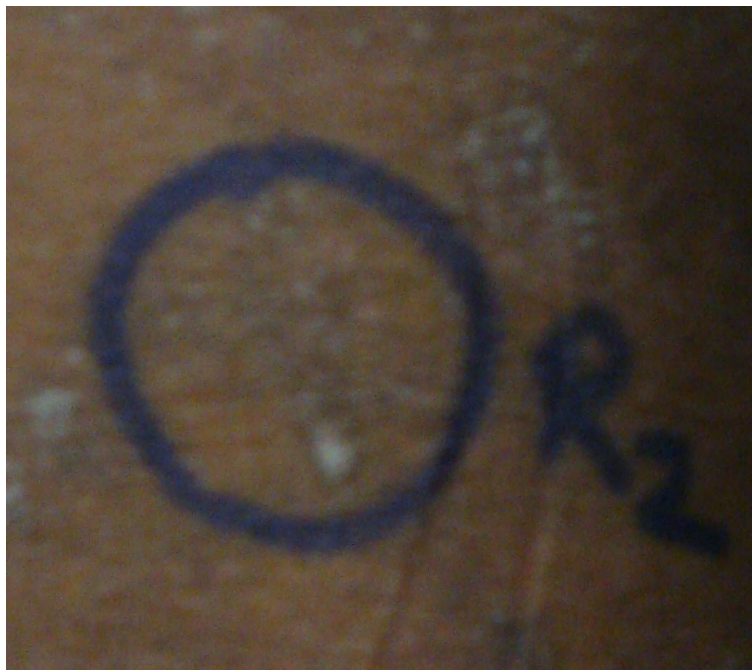


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AFTER TEN SESSIONS



AFTER FIFTEEN SESSIONS



Discussion

Phototherapy treatment for psoriasis has been extensively modified since the landmark combination of UVB and topical tar emollient was introduced by Goeckerman in 1925.

Although PUVA is considered one among the most effective therapeutic modality for psoriasis, it may causes nausea, requires the use of eye protection after treatment sessions, cannot be used during pregnancy, is contraindicated in patients with significant hepatic impairment or taking warfarin or phenytoin, and requires the some what inconvenient previous administration of psoralen. Of greatest concern, is the potential of PUVA to cause nonmelanoma skin cancer after 160 to 200 lifetime treatments, which almost certainly exceeds by some margin that of a comparable number of NB-UVB sessions ^[93,94] and certainly of broadband UV-B sessions^[95].

NbUVB has not been uniformly effective for all cases of chronic psoriasis. Similarly PUVA also has failure rates. Since the absorption spectra of psoralen (325nm) is closer to 311nm, and considering the emission spectra of TL01 lamps of 311nm, it is possible that NbUVB may be effective like PUVA when combined with psoralen.

It is also possible that the combination of Psoralen and NbUVB may reduce

the dose required of either psoralen or NbUVB or both thus minimizing the side effects. UVB is mostly effective when administered three times a week, whereas PUVA is usually administered twice a week^[95]. Thus it is possible that combination might also reduce the frequency of phototherapy thereby reducing the inconvenience, the cost and reduction in total cumulative dose of NbUVB.

The mean age in our study was 49 years out of which 15 were men and 2 were women. Our patients belonged to Type IV/ V/ VI skin (one – IV, fourteen- V, two -VI). The mean MED of our study was 457mj. Various studies have recorded different values of MED depending on the patient's skin type. In a study done by Serisha et al MED values of 33 individuals ranged from 300mj to 1700mj with mean MED of 714.15mj/cm² whereas in another study conducted among the Caucasian skin on 11 patients with psoriasis of skin types I, II and III the MED for NbUVB ranged from 135mj/cm² to 540mj/cm² with mean value of 293mj/cm²^[96,97]

We started with the initial dose of 70% of the MED and a Baseline Total Lesional Severity Scale(TLSS) Scoring was calculated for each patient. The initial dose when compared to other studies varied from 0.03J/cm² to 0.7J/cm² where MED values were not determined to initiate the treatment^[91,92]. In our study , the treatment was given thrice weekly for five weeks (15 sittings) with

10% increment following each dose and the TLSS scoring was calculated before starting the treatment(Baseline) and at the end of five, ten and fifteen treatments . The mean TLSS score after the treatments were reduced in NbPUVB when compared to NbUVB after 10 sessions and this value (p value = 0.006)was statistically significant. However by the end of our study, after 15 treatments there was no stastical difference between NBUVB & NbPUVB(p value = 0.837).

In a similar study conducted by Sakuntabhai et al wherein the MED was not determined and the initial dose was $0.7\text{J}/\text{cm}^2$ and the increment was 40 % after each dose given at twice weekly intervals for all patients. They concluded that psoralen enhanced the therapeutic efficacy when combined with NbUVB as compared to NbUVB alone^[92]

In another study conducted by Morrison WL et al comparing the therapeutic effects of broad band UVB (FS-40 sunlamp bulbs) radiation versus UVB radiation plus methoxsalen in 10 cases of psoriasis, they concluded that there was no detectable difference in the response between UVB plus methoxsulen and UVB phototherapy alone^[91].

Subsequently we are planning to measure the minimal phototoxic dose (MPD) to NbUVB following administration of oral psoralen.

Conclusion:

We conclude that addition of psoralen does not increase the efficacy of
Narrow Band UVB

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MASTER CHART

S.NO	Name	Age	Sex	MED	Initial Dose	Total Cumulative Dose	Number of Treatments
1	Vinayagam	37	Male	750mj	525mj	16588mj	15
2	Sundararajan	62	Male	500mj	350mj	11064 mj	15
3	Ariniyarajan	31	Male	500mj	350mj	11064 mj	15
4	Duraisamy	70	Male	300mj	210mj	7249 mj	15
5	Subramaniam	69	Male	950mj	660mj	20903 mj	15
6	Suresh Kumar	57	Male	500mj	350mj	11064 mj	15
7	Logaswaran	54	Male	250mj	175mj	5500 mj	15
8	Raja	34	Male	450mj	315mj	9888 mj	15
9	Subramanian	33	Male	300mj	210mj	7249 mj	15
10	Muthulakshmi	59	Female	400mj	280mj	10953 mj	15
11	Nirmala	46	Female	500mj	350mj	11064 mj	15
12	Kumaraguru	51	Male	350mj	245mj	7710 mj	15
13	Karthikeyan	35	Male	300mj	210mj	7249 mj	15
14	Rajamanickam	48	Male	350mj	245mj	Lost for Follow-up	2
15	Yuvaraj	52	Male	300mj	210mj	974 mj	4
16	Palanisamy	25	Male	250mj	175mj	810 mj	4
17	Karupasamy	48	Male	350mj	245mj	2783 mj	8